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DICLOFENAC SUBMICRON PARTICLE CAPSULES DEMONSTRATE EARLY AND SUSTAINED ACUTE PAIN RELIEF IN A PHASE 3 STUDY IN PATIENTS FOLLOWING BUNIONECTOMY SURGERY

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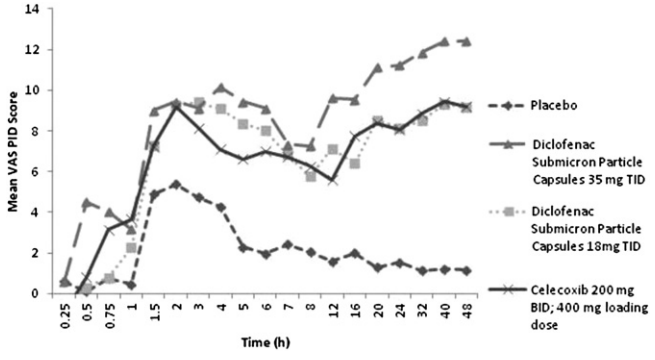
Purpose: Early management of acute pain may impact the severity and duration of pain. NSAIDs are utilized to treat acute pain but have the potential for serious dose-related gastrointestinal, cardiovascular, and renal adverse events (AEs). Investigational submicron particle NSAIDs using proprietary SoluMatrix™ technology are being evaluated to assess the potential to provide effective pain relief at lower doses than currently available oral NSAIDs. In a Phase 1 study, diclofenac submicron particle capsules 35 mg achieved an early time to maximum concentration, a similar maximum concentration, and lower systemic drug exposure compared with diclofenac potassium immediate-release tablets. In a Phase 2 study, diclofenac submicron particle capsules (18 and 35 mg) provided effective analgesia and were generally well-tolerated in a validated post-surgical model of mild to moderate pain. We evaluated the analgesic efficacy of diclofenac submicron particle capsules in a post-surgical model of moderate to severe pain.
Methods: This Phase 3 multi-center, double-blind study enrolled 428 patients 18-65 years of age who underwent a primary, unilateral first metatarsal bunionectomy with osteotomy and fixation under regional anesthesia. Patients experiencing a pain intensity rating of ≥40mm on a 100mm visual analog scale (VAS) were randomized to receive diclofenac submicron particle capsules (18 or 35mg; TID), celecoxib (400mg loading dose, then 200mg BID), or placebo. The primary endpoint was the summed pain intensity difference measured by VAS over 48 hrs (VAS SPID-48). Secondary endpoints included the VAS pain intensity difference (VAS PID) at various time points versus placebo.
Results: As presented recently for the primary endpoint (mean VAS SPID-48), diclofenac submicron particle 35mg (524; $P<0.001$) and 18mg (393; $P=0.01$) and celecoxib (391; $P=0.011$) demonstrated significant pain control compared with placebo. Some pain relief (mean VAS PID) was apparent in the diclofenac submicron particle 35mg (4.52) group at 30min in contrast to the placebo (0.12) group. Pain control increased over time for all active treatment groups. At 4h after dose administration, diclofenac submicron particle 35mg provided better pain control (VAS PID) versus placebo ($P=0.025$; **Figure**). At 5h after study entry, significant pain control was noted in the diclofenac submicron particle 35mg (9.43; $P=0.002$), 18mg (8.35; $P=0.009$), and celecoxib (6.62; $P=0.032$) treatment groups versus placebo (2.30; **Figure**).Overall, the most frequent treatment-emergent adverse events were localized post-procedural edema (32.7%, 140/428), nausea (29.7%, 127/428), headache (12.9%, 55/428), and dizziness (11.7%, 50/428).



Conclusions: Lower-dose, submicron particle diclofenac demonstrated better pain control at 48h (VAS SPID-48) with evidence of analgesia as early as 30 min after administration compared with placebo, and was generally well tolerated. These results suggest that diclofenac submicron particle capsules are a potentially promising therapeutic option for acute pain.

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MANAGEMENT OF PATIENTS WITH KNEE OSTEOARTHRITIS BEFORE AND AFTER THE PHILIPPINE CLINICAL PRACTICE GUIDELINE FOR KNEE OSTEOARTHRITIS

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Purpose: We aim to review changes in physicians' practice on the management of osteoarthritis (OA) before and after the publication of the Philippine Rheumatology Association (PRA) Clinical Practice Guidelines (CPG) for knee OA in year 2010. Major highlights of the CPG were advocacy of paracetamol as first-line pharmacologic therapy followed by tramadol, good evidence for usage of glucosamine sulfate, limitation of NSAIDs usage, and emphasis on rehabilitation and lifestyle modification/advice.
Methods: This study reviewed clinical charts of patients diagnosed with primary OA (American College of Rheumatology criteria) in the Philippine General Hospital Arthritis Clinic from January to December 2009 and January to December 2011. Data regarding conventional management (non-pharmacologic and pharmacologic) and complementary/alternative therapies on the first visit were extracted. Continuous data were described using means and standard deviations while nominal data were described using frequencies and percentages. T-test for two proportions were used to compare use of different pharmacologic and alternative treatment pre- and post- CPG. P-value less than 0.05 were considered significant.
Results: One hundred eleven patients were included in the study (60 from 2009 and 51 from 2011). Mean age of symptom presentation and diagnosis were 59.7 years (SD: 10.3 years) 63.2 years (SD: 9.9 years), respectively. Majority (81.08%) were females. Mean BMI was 26.5 kg/m2 (SD: 5.03), considered obese stage I. The most common presentation was knee pain (69.8%), majority (76.48%) of which were bilateral. There were no significant differences (p-value 0.723) between the mean age between pre- (mean 59.3 years; SD 1.5 years) and post-CPG patients (mean 60.1 years; SD 1.3 years). Likewise, there were no significant differences in sex (p-value 0.2529) and proportion of dyspeptics (p-value 0.4760). Mean BMI is higher among pre-CPG patients (mean 27.9; SD 0.78) compared to post-CPG (mean 25.69; SD 0.56) and the result is statistically significant (p-value 0.03). There were statistically more patients post-CPG who had Kellgren Lawrence score of 2 compared to pre-CPG patients. The two populations had no significant difference across the rest of the scores. The use of paracetamol is significantly higher among post-CPG patients (54/60, 90% vs pre-CPG 33/51, 64.71%; p-value 0.0013) but the use of tramadol before and after CPG publication is not statistically significant (p-value 0.1119). Use of NSAID (COX-1 inhibitor) and COX-2 inhibitors was significantly lower after the CPG publication [(5/60, 8.33% vs pre-CPG 17/51, 33.33%; p-value 0.013) and (6/60, 10.17% vs pre-CPG 25/51, 49.02%; p-value 0.000), respectively]. Glucosamine sulfate use was slightly higher post-CPG (31/51, 51.67%) compared to pre-CPG (25/60, 49.02%) but this difference was not statistically significant (p-value 0.7810). Use of non-pharmacologic interventions was significantly higher post-CPG (49/60, 81.67% compared to pre-CPG 12/51, 23.53%, p value 0.0000).
Conclusion: The published CPG by the PRA significantly changed the physicians' management of patients with OA. Whether it has impacted the patients' symptoms, quality of life and overall satisfaction, however, remains to be determined and can be the subject of studies in the near future.

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A SINGLE INTRA-ARTICULAR INJECTION WITH IL-4 PLUS IL-10 AMELIORATES BLOOD-INDUCED CARTILAGE DEGENERATION IN HAEMOPHILIC MICE

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Purpose: Exposure of joint cartilage to blood can occur after joint trauma, during or after major joint surgery, or due to hemophilia. This ultimately leads to joint damage, both by direct effects of blood on cartilage and via synovial inflammation (Lafeber et al., Haemophilia 2008). The cytokines interleukine (IL)-4 and IL-10 are known as modulatory cytokines. A combination of IL-4 plus IL-10 protects against blood-induced cartilage damage *in vitro* (van Meegeren et al., Osteoarthritis & Cartilage 2012). It has been hypothesized that the combination

of both cytokines is effective early in the process of cartilage damage. In this study it is investigated whether a single intra-articular injection of IL-4 plus IL-10 immediately after a joint bleed limits cartilage damage in an *in vivo* haemophilia mouse model.

Methods: Factor VIII knockout mice were punctured once with a needle below the patella to induce a joint bleed. Subsequently IL-4 plus IL-10 (n=24) or vehicle (n=24) was injected intra-articularly once. After 35 days, the knee joints were examined for cartilage damage by macroscopic and microscopic evaluation using the OARSI histopathology score specific for mice for cartilage degeneration and the Valentino score for synovial inflammation. The left knee joint in both groups served as an unaffected control.

Results: Induction of a joint bleed led to a significant increase in macroscopic remains of a joint bleed and to an increase in joint diameter in both groups compared to the unaffected joints (all $p<0.05$ compared to control). Although not statistically significant, the IL-4 plus IL-10 injected joints tended to present less remains of a joint bleed compared to the vehicle injected joints (46% versus 58%; p=0.386). Moreover, the diameter of the joints injected with IL-4 plus IL-10 tended to be smaller than that of the vehicle injected joints (2.63±0.16mm vs 2.91±0.29mm; p=0.174). After a joint bleed, the OARSI score as well as the Valentino score increased compared to the unaffected joints. Intra-articular injection of IL-4 and IL-10 ameliorated cartilage degeneration caused by the joint bleed (mean change in OARSI score in experimental joint compared to control joint for vehicle injection 0.9±1.2 (p=0.010) and for IL-4 plus IL-10 injection 0.5±1.8 (p=0.216)). No effect on inflammation was observed at 35 days after the joint bleed for IL-4 plus IL-10 compared to vehicle (mean Valentino score after IL-4 plus IL-10 injection 3.6±1.8 and for vehicle injection 2.9±2.0 (p=0.220)).

Conclusion: A single intra-articular injection of IL-4 plus IL-10 directly after a single joint bleed limits cartilage degeneration, but not synovial inflammation. Improved bioavailability of both cytokines might improve the protective ability of both cytokines in development of cartilage degeneration, and probably also inflammation.

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DIFFERENT CHANGES IN THE BIOMARKER CTX-II FOLLOWING INTRA-ARTICULAR INJECTION OF HIGH MOLECULAR WEIGHT HYALURONIC ACID AND ORAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS FOR PATIENTS WITH KNEE OSTEOARTHRITIS: A MULTI-CENTER RANDOMIZED CONTROLLED STUDY

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Purpose: Intra-articular injections of hyaluronic acid (IA-HA) and oral non-steroidal anti-inflammatory drugs (NSAIDs) are both recommended by OARSI for the management of knee OA. However, their molecular effects on the pathophysiology of knee OA remain unclear. A C-terminal telopeptides of type II collagen (CTX-II) is biomarker discovered as a marker of type II collagen degradation. Recently, CTX-II has found to originate primarily from the interface between subchondral bone and articular cartilage which is a site of potential remodeling in OA. The regulation of CTX-II release is more reflective of bone rather than cartilage metabolism. The aim of this study, the subanalysis of the multicenter RCT [the result of the primary endpoint (OARSI 2012)] was to compare the changes of CTX-II in response to IA-HA to those in response to NSAID treatment for knee OA.

Methods: A total of 200 patients with knee OA (K/L 1 to 3) were registered from 20 hospitals and randomized to IA-HA (High molecular weight 2,700 kDa HA) or NSAID (loxoprofen sodium). For patients treated with NSAID, they used NSAID 3 tablets (180 mg)/day for 5 weeks. For patients treated with IA-HA, IA-HA was conducted 5 times at one week intervals. The fasted second void urine samples collected from all patients were stored at -80Co until analysis. uCTX-II levels were corrected for urine creatinine concentration. The CTX-II data were analyzed by the per protocol set (PPS).

Results: Half (100) of the patients were randomly allocated into the NSAID group, and the other half allocated into the IA-HA group. After the 5 week treatment period, 68 of 100 of the patients in the IA-HA group and 58 of 100 of those in the NSAID group were eligible for CTX-II analysis. At baseline, no significant differences of baseline characteristics were observed between IA-HA and NSAID groups. The Japanese Knee Osteoarthritis Measure (JKOM) score of the patients in both the IA-HA (-37.4%) and NSAID (-35.3%) groups were significantly reduced following treatment ($p<0.001$). The difference in the percent changes of the JKOM score between the two intervention arms was -2.1% (90%CI; -10.9 to 6.2%), demonstrating the non-inferiority of IA-HA to the NSAID for the reduction in the clinical symptoms. uCTX-II levels were significantly reduced by the NSAID treatment. In contrast, uCTX-II levels were significantly increased by the IA-HA treatment. The percent changes of uCTX-II by IA-HA treatment (11.6%) were significantly different than those of that by NSAID treatment (-9.0%) ($p<0.0001$). When the patients were analyzed based on the radiographic severity of knee OA, the differences of uCTX-II responses between the NSAID and IA-HA were again observed.

Conclusions: We observed in this RCT that IA-HA treatment increased uCTX-II levels, while oral NSAID reduced uCTX-II levels, while both treatments improved symptoms of pts. with knee OA. The differences in biomarker response suggest different modes of action, each with a beneficial effect on symptom: one being stimulatory of cartilage/bone interface extracellular matrix type II collagen turnover (IA-HA) and the other reducing such turnover.

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PHARMACOKINETICS OF A THERMALLY RESPONSIVE CURCUMIN CONJUGATE FOR LOCAL ANTAGONISM OF NEUROINFLAMMATION IN DISC HERNIATION

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Purpose: Tumor necrosis factor alpha (TNFα) is believed to be a key mediator of inflammatory events associated with herniated intervertebral disc (IVD). Local delivery of TNF antagonists via epidural injections to treat pain or dysfunction associated with herniated IVD has been studied in the clinic with some success. We hypothesize that sustained release of injectable depots containing cytokine antagonists can be a safer, cost-effective treatment for relieving pain associated with IVD herniation. We have designed novel drug conjugates comprised of elastin-like polypeptides (ELP) and a small anti-inflammatory compound, curcumin, which has an excellent safety profile in clinical trials. ELPs are biocompatible, biodegradable polymers that are soluble below a transition temperature (Tt,) and form micron-sized depots above Tt. Here, we report on the pharmacokinetics and clearance rates of injectable, ELP-curcumin conjugate 'depots' delivered to the perineural space in mice.

Methods: A novel derivative of curcumin, monofunctional curcumin carbamate (MCC, Fig 1), was chemically coupled to glutamate-containing ELPs (Fig 2). Drug-carrier ratio, conjugate purity, Tt, and hydrodynamic radius (Rh) were quantified with UV-Vis, RP-HPLC, and dynamic light scattering. In vitro bioactivity of conjugates against TNFα-induced proliferation was quantified with L929 cells as previously described. For in vivo studies, the right sciatic nerve of C57BL/6 female mice (n=3 per group, 12 weeks old) was surgically exposed, and curcumin or ELP-MCC (25µl, 150nmol) was delivered to the perineural space. Blood was collected at times from 0.5 to 168 hours and tissues were harvested at varying sacrifice times from 2 to 168 hours. Plasma and solubilized tissue was analyzed for curcumin presence via fluorescence.

Results: ELP-MCC conjugates were synthesized and characterized to have mean drug-carrier ratios of 5.7 to 1 (MW=37.8kDa), >90% purity,